REMARKS

Claims 1-3, 5, 7 and 9-13 were pending and under consideration in the July 1, 2003 Offic Action. Claims 1, 2 and 5 have been amended herein to m re clearly point out that which Applicants regard as the invention. Specifically, Claim 1 has been amended to delete the phrase "for a time sufficient to induce apoptosis in a cell exhibiting normal acid sphingomyelinase activity" as requested by the Examiner. Claims 1, 2 and 5 have been amended to incorporate the steps of (a) and (b) into a single step (a) as requested by the Examiner. Applicants have amended Claims 7 and 9 to correct claim dependency. No new matter has been added by the present amendments. Accordingly, after entry of the instant amendment, Claims 1-3, 5, 7 and 9-13 will be pending and under consideration.

INTERVIEW SUMMARY

At the outset, Applicants' representatives wish to thank Supervisory Primary Examiner Christina Chan and Primary Examiner Phuong N. Huynh, Ph.D. for the courtesy of the telephonic interview of October 27, 2003 with Stephen K. Sullivan and Henry P. Wu, in connection with the above-referenced application. During the Interview, Dr. Sullivan presented arguments as to why the instantly claimed invention was not indefinite under 35 U.S.C. § 112 or made obvious under 35 U.S.C. § 103 by the prior art relied upon in the July 1, 2003 Office Action. Examiner Huynh agreed to reconsider her rejections in view of these arguments upon filing of the present reply and also agreed to supply a signed and initialed PTO-1449 form indicating consideration of **References CK** and **CL** previously submitted. Details of the interview are presented below.

THE REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 2, 3 and 5 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner alleged that "exposing the cell" as recited in Claims 2 and 5 is indefinite because it is not clear which cell is being exposed.

In the telephonic interview of October 27, 2003, Examiner Huynh suggested that the rejection could be overcome by amending the claim to recite "exposing said cell" or "exposing said acid sphingomyelinase-deficient cell". In a follow-up teleph n call of October 28, 2003, Examiner Huynh suggested an alternative amendment for Claims 1, 2

and 5 to overcome the rejection. Specifically, Examiner Huynh suggested, for Claims 2 and 5, combining steps (a) and (b) to parallel step (c) and, for Claim 1, deleting the phrase "for a time sufficient to induce apoptosis in a cell exhibiting normal acid sphinogmyelinase activity" in steps (b) and (c).

Without conceding the correctness of the rejection, Applicants have amended Claims 1, 2 and 5 in accordance with the Examiner's suggestions.

In view of the foregoing, Applicants respectfully request withdrawal of this rejection.

THE REJECTION UNDER 35 U.S.C. § 103(a)

Claims 1-2, 5 and 9-11 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Jafferzou *et al.*, 1992, Cancer Research 52:6440-6446 ("*Jaffrezou*") in view of Lowe *et al.*, 1993, *Cell* 74:957-67 ("*Lowe*"), Jarvis *et al.*, 1994, *Proc. Natl. Acad. Sci. USA* 91:73-77 ("*Jarvis*"), Cifone *et al.*, 1995, *EMBO J.* 14: 5859-68 ("*Cifone* I") and Cifone *et al.*, 1994, J. Exp. Med. 180: 1547-1552 ("*Cifone* II")

Claims 3, 7 and 12-13 were rejected under 35 U.S.C. § 103(a) as being unpatentable over *Jaffrezou* in view of *Lowe, Jarvis, Cifone* I and *Cifone* II as applied to Claims 1-2, 5 and 9-11, and further in view of U.S. Patent No. 5,773,278 ("*Schuchman*") or Horinouchi *et al.*, 1995, *Nature Genetics* 10: 288-93 ("*Horinouchi*") or Otterbach *et al.*, 1995, *Cell* 81:1053-61 ("*Otterbach*").

In response, Applicants respectfully traverse the rejection. None of the cited references, either alone or in combination, teach or suggest the invention as defined in the claims now pending for the reasons of record and as set forth below. The objective standard for obviousness under 35 U.S.C. § 103 and references *Lowe*, *Jarvis*, *Cifone* I, *Schuchman*, *Horinouchi* and *Otterbach* have been previously discussed.

In the telephonic interview of October 27, 2003, Applicants' representatives submitted that **References CK and CL** (of record) were provided to show that, at the time of the present invention, it was not at all clear in the art which sphingomyelinase was involved in apoptosis. While Examiner Huynh pointed to Figure 4 of newly-cited *Cifone* II as evidence that acidic sphingomyelinase was involved in apoptosis, Dr. Sullivan argued

that the prior art as a whole must be considered[1]. Examiner Huynh agreed to reconsider the rejection in view of **References CK and CL.**

As previous noted in Applicants' December 9, 2002 reply, **Reference CK** demonstrates that exposure to the chemotherapeutic agent daunorubicin is mediated by a neutral sphingomyelinase (see the Abstract). **Reference CL** reviews a number of references that had been published at the time of the invention and cites a series of observations that strongly suggest that stress-induced apoptosis is not endolysosomal (see the Abstract).

In the telephonic interview of October 27, 2003, Applicants' representatives further submitted that none of the cited references teach or suggest methods for identifying compounds which increase or decrease a cell's sensitivity to acid sphingomyelinase-related apoptosis. Examiner Huynh responded that *Lowe* teaches a p53 deficient cell line which is similar to an acid sphingomyelinase deficient cell line. Applicants reiterated that *Lowe* does not teach methods to identify any compounds. In fact, *Lowe* demonstrated that p53, not any "test compounds", can modulate a cell's sensitivity to chemotherapeutic agent stress stimuli.

The Examiner asserted that *Cifone* I teaches that it is of interest to screen for compounds which increase or decrease a cell's sensitivity to acid sphingomyelinase related apoptosis (citing page 5865, col. 2). In fact, *Cifone* I only teaches that it is of interest to determine possible targets for pharmacological correction of apoptosis (see page 5865, col. 2, lines 25-34).

With respect to newly-cited reference *Jaffrezou*, it does not teach methods to identify compounds, much less methods to identify compounds that increase or decrease a cell's sensitivity to acid sphingomyelinase-related apoptosis. In fact, *Jaffrezou* demonstrated that an inhibitor of acid sphingomyelinase caused sequestration of doxorubicin in intracellular vesicles (see the Abstract).

Accordingly, Applicants respectfully request reconsideration of the rejection.

---

[1] The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. *In re Hedges*, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986).

CONCLUSION

Applicants respectfully request entry and consideration of the foregoing amendments and remarks. An early allowance is earnestly sought. No fee is believed to be due in connection herewith. If any fee is due, however, please charge the required fee to Pennie & Edmonds LLP Deposit Account No. 16-1150.

Respectfully submitted,

Dated: November 3, 2003

Geraldine F. Baldwin 31,232
Geraldine F. Baldwin (Reg. No.)

By: Stephen K. Sullivan 43,171
Stephen K. Sullivan (Reg. No.)

PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, New York 10036-2711
(212) 790-9090